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CLINICAL PERSPECTIVE

Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia?*

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ABSTRACT

Several recent publications have drawn attention to the role of the thyroid hormone status of the mother on the future neuropsychological development of the child. The screening of pregnant women for clinical or subclinical hypothyroidism based on second trimester elevated maternal TSH values has been proposed. Here, we have summarized present epidemiological and experimental evidence strongly suggesting that conditions resulting in first trimester hypothyroxinemia (a low for gestational age circulating maternal free T_4, whether or not TSH is increased) pose an increased risk for poor neuropsychological development of the fetus. This would be a consequence of decreased availability of maternal T_4 to the developing brain, its only source of thyroid hormone during the first trimester; T_4 is the required substrate for the ontogenically regulated generation of T_3 in the amounts needed for optimal development in different brain structures, both temporally and spatially. Normal maternal T_3 concentrations do not seem to prevent the potential damage of a low supply of T_4, although they might prevent an increase in circulating TSH and detection of the hypothyroxinemia if only TSH is measured. Hypothyroxinemia seems to be much more frequent in pregnant women than either clinical or subclinical hypothyroidism and autoimmune thyroid disease, especially in regions where the iodine intake of the pregnant woman is inadequate to meet her increased needs for T_4. It is proposed that the screening of pregnant women for thyroid disorders should include the determination of free T_4 as soon as possible during the first trimester as a major test, because hypothyroxinemia has been related to poor developmental outcome, irrespective of the presence of high titers of thyroid autoantibodies or elevated serum TSH. The frequency with which this may occur is probably 150 times or more that of congenital hypothyroidism, for which successful screening programs have been instituted in many countries. (*J Clin Endocrinol Metab* 85: 3975–3987, 2000)

THE RECENT PUBLICATION by Haddow *et al.* (1) on "Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child," has drawn new attention to the relationship between maternal thyroid deficiencies and the future neuropsychological development of her child. This is a very important issue that has, unfortunately, been somewhat misunderstood for decades, to the point that Mestman (2) unexpectedly found that in a recent study from Los Angeles involving 78 women who were hypothyroid at booking into the clinic, 34 (44%) had discontinued thyroid therapy at the time they discovered they were pregnant "some after receiving advice from their own health care professionals, and others because of concern for the potential harmful effect of thyroid medications on the conceptus."

As a consequence of the report by Haddow *et al.* (1) and other (3) recent studies, the possibility of avoiding potentially preventable alterations of neuropsychological development by screening pregnant women for maternal thyroid hormone deficiencies is being discussed. Even before this new evidence was presented relating maternal thyroid status with mental development of the child, screening for thyroid disfunctions during pregnancy had already been advocated because of their frequency and risk for the mother's health and for the outcome of pregnancy (4).

Because such programs are not easily implemented, we believe the present comments may be pertinent to obtain the maximum benefits for the largest number of children.

Maternal thyroid hormone deficiencies and fetal neurodevelopment

Aim. Our aim is to clarify whether the principal factor leading to poorer neurodevelopment of the child is: 1) maternal hypothyroidism, whether clinical or subclinical, as defined by TSH higher than the 98th percentile of the normal population (1); or 2) maternal hypothyroxinemia *per se*, whether or not TSH is increased (3).

We will review, albeit in very condensed form, relevant information obtained from epidemiological, clinical, and basic science studies that strongly suggest that maternal thyroid status, especially in early pregnancy, is causally related to the survival and neuropsychological development of the offspring.

Reports from human populations with severe iodine deficiency (ID). After prolonged observations of cretins born in areas

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with endemic goiter, an important role of maternal thyroid function was suspected "it is of the greatest importance to inquire into the ante-natal history of all backward children and to examine the mother for thyroid defect" (5).

Not until 1965, however, were data presented that suggested that the inability of the mothers to increase their low circulating T_4 during pregnancy was causally related to the birth of cretins (6). Thereafter, numerous groups (see Table 1) presented convincing evidence that maternal hypothyroxinemia early in pregnancy is not only the cause of reproductive failure and the birth of neurological cretins, but also of less severe mental deficits that affect a large proportion of the apparently "normal" (noncretin) population of the same area. These deficits, as well as the birth of cretins, are irreversible consequences of the ID and can only be prevented within the first months of gestation with an adequate supply of iodine. This finding is in conceptual agreement with the very early (first trimester) development of cerebral structures that are characteristically affected in neurological cretinism. Two other findings are quite important in the present context: namely, that the motor and cognitive impairment of the progeny was correlated with the degree of maternal hypothyroxinemia, and not with circulating T_3 or TSH levels; and that these hypothyroxinemic women are not clinically hypothyroid, because of their relatively normal circulating T_3.

Reports from human populations without severe ID. Table 2 summarizes relevant information from studies carried out in areas without severe ID, which have suggested an important role of maternal T_4 in the outcome of the pregnancy and in the neuropsychological development of the progeny, and which have provided increasing evidence that is the critical factor is maternal hypothyroxinemia early in gestation.

The concept of "hypothyroxinemia" of the pregnant woman was defined by Man and *et al.* (18–21) as a circulating level of T_4 [then measured as butanol extractable iodine (BEI)], below the normal range for women in the same trimester of pregnancy, whether or not "clinical hypothyroidism" was evident. These pioneering studies not only drew attention to the decreased mental development of the progeny of hypothyroxinemic women but also reported that this negative effect was prevented by adequate and early correction of the maternal hypothyroxinemia with thyroid preparations.

Table 2 also includes reports regarding the increased proportion of unsuccessful or complicated pregnancies in hypothyroxinemic women (*i.e.* spontaneous abortions, premature births, major complications at delivery, perinatal deaths, congenital malformations) and their relation to first trimester low free T_4 (FT_4), but not to FT_4 near term; early treatment to prevent such complications has been stressed (22).

During the last decade, Pop *et al.* (23) have drawn attention to an average impairment of 10.5 IQ points in the offspring of mothers with high thyroid peroxidase antibody (TPO-Ab) titers during pregnancy. They have later reported (3) that in normal pregnancies a maternal FT_4, at 12 weeks of gestation, which is equal to or less than the 10th percentile of first trimester values (10.4 pmol/L in their series), is associated with distinctly impaired psychomotor infant development at the age of 10 months, whether or not TSH and TPO-Abs were elevated. They have confirmed this is an ongoing prospective study (24), comparing developmental indices, determined at 3 weeks and 1 and 2 yr of age, with maternal FT_4. Smit *et al.* (25) have found a similar relationship between first trimester FT_4 and the early neurodevelopment of children born from treated hypothyroid women. These studies (3, 25) did not find significant correlations when the neurodevelopmental outcome was related to maternal TSH, or to FT_4 later in gestation.

The finding that FT_4 levels after midgestation are not correlated with the developmental outcome does not mean that

TABLE 1. Brief description of some major pioneering findings from studies in areas with severe ID

Major findings	Year	Main references	Based on
Suggest maternal thyroid defects when the child is mentally retarded.	1915 1917	Switzerland (7) Himalayas (5)	Extensive clinical observations in areas with severe ID.
Neurological cretinism is related to the low circulating T_4 of pregnant women who are not clinically hypothyroid.	1965	Papua, New Guinea (6)	PBI was used as measure of T_4.
The birth of cretins is prevented by iodization of pregnant women before pregnancy, or very soon after its onset.	1971	Papua, New Guinea (8)	Controlled double-blind epidemiological study.
Neurodevelopment of the noncretin population is also affected and only prevented by iodization before midgestation.	1974	Perú (9, 10), China (11)	Controlled iodization program with measurements of maternal serum PBI, T_4 or FT_4, and IQ of progeny.
Neurodevelopment of the noncretinous progeny is significantly correlated to maternal T_4, but not to T_3 or TSH.	1976	Papua, New Guinea (12–15)	Determinations of maternal T_4, FT_4, T_3 and TSH, and psychometric testing of progeny.
Low maternal T_4 is causally related to "reproductive failure."	1980	Review (16)	Described for women with hypothyroidism and for women from ID areas.
Brain structures, that are severely affected in neurological cretinism, develop before midgestation.	1989	Review (17)	Neurological examination of cretins from ID regions in different continents.

PBI, Protein-bound iodine, mainly I in the form of T_4; reproductive failure, increased proportions of spontaneous abortions, premature births, major complications at delivery, perinatal death, and congenital malformations.

TABLE 2. Major findings from studies in areas without known ID

Major findings	Year	Main references	Based on
"Reproductive failure"[a] of hypothyroid women.	1962	U.S.A. (20, 26, 27), Belgium (4)	Maternal BEI, T_4, FT_4, TSH.
Reproductive failure related to 1st trimester low FT_4.	1995	U.S.A. (22)	FT_4, TSH.
Maternal "hypothyroxinemia" is related to low IQ of progeny; both corrected by treatment (during pregnancy).	1967	U.S.A. (18–21, 28, 29)	IQ of the progeny at 7 yr of age, compared with maternal BEI, with and without treatment.
Maternal thyroid anti-TPO antibodies during pregnancy related to lower IQ of progeny.	1995	The Netherlands (23)	IQ of progeny, maternal T_4, FT_4, TSH, anti-TPO.
Psychomotor development is correlated to 1st trimester FT_4 ≤10th percentile, not to TSH, anti-TPO, or 3rd trimester FT_4.	1999	The Netherlands (3, 24)	Psychomotor and mental development at 3 weeks to 2 yr of age, FT_4, TSH, anti-TPO.
Increased risk of poor neuropsychological scores in progeny of women with maternal TSH ≥98th percentile.	1999	U.S.A. (1)	IQ scores of progeny of women with 2nd trimester maternal TSH ≥98th percentile.

[a] Increased proportions of spontaneous abortions, premature births, major complications at delivery, perinatal death, and congenital malformations.

after midgestation the protective effect of maternal T_4 has been lost, or that the fetal brain no longer requires thyroid hormone. Prompt postnatal treatment of athyrotic babies prevents the severe mental retardation that was associated with this condition when onset of treatment was delayed (30). This very positive result of Neonatal Screening Programs has been quoted as argument that the human fetal brain does not require thyroid hormone for normal development before birth (31). But, an alternative explanation is that the fetal brain has been protected by the normal thyroid status of their mothers. Indeed, when maternal thyroid status is not normal throughout gestation and fetal thyroid function is also impaired, neurological damage and mental retardation of the child can be as severe as in neurological cretinism, despite immediate postnatal treatment of the baby with T_4 (17, 32–35).

Reports of poor developmental outcome in many babies faced with a premature interruption of the maternal supply of thyroid hormone—occurring when their thyroid is still quite immature (36)—also indicate that the fetal brain needs thyroid hormone throughout gestation and that a normal supply of maternal T_4 has an important protective role after midgestation. The data from two such studies (37, 38) show a direct relationship between the degree of neonatal hypothyroxinemia and future neurodevelopment of the progeny. Both neurological dysfunction at 5 yr of age and school failure at 9 yr of age were significantly related to lower T_4 levels during the neonatal period (37). Even after correction for other perinatal confounding factors, there was a statistically significant 30% increase in the odds of neurological dysfunction and school failure for each decrease of the T_4 level by 1 SD. In the second study (38), the odds ratio for increased cerebral palsy in preterm infants with neonatal hypothyroxinemia increased more than 4-fold (after correction for many possible confounding factors), with a mean reduction of 7 points in the mental developmental score at 2 yr of age. The postnatal FT_4 of premature babies, lower than that of fetuses of comparable age still *in utero*, is usually not accompanied by an elevation of circulating TSH (39), and a correlation is not found between neurodevelopmental outcome and neonatal TSH levels. Thus, in these babies, the critical factor for the prediction of future neurodevelopmental problems is the degree of their neonatal hypothyroxinemia, and not hypothyroidism, as detected by elevated circulating TSH. The degree of the hypothyroxinemia not only depends on gestational age and immaturity of the thyroid gland of the newborn, but is also increased by a low iodine intake (40). There is, however, no information regarding a possible relationship with the thyroxinemia of their mothers up to birth, but it seems plausible that maternal hypothyroxinemia, especially when related to ID, would only increase the difficulties encountered by the newborn in meeting postnatal hormone requirements, including those of the developing brain.

Information from basic research. The possible protective role o the maternal transfer of thyroid hormone to the fetus wa actually not actively disputed until the mid-1960s and earl 1970s (41–43). However, during the following decades th general consensus became that the placenta is virtually im permeable to the iodothyronines and that the small amount possibly transferred would be of no physiological impor tance, either in health or disease, ideas that were supporte by experiments involving sheep. The prevailing idea tha there is no biologically significant transfer of thyroid hor mones throughout gestation (including the first trimester and that these hormones would not be required for norma early (or late) fetal brain development is likely to have con tributed to a general lack of understanding and acceptanc of the results from the epidemiological and clinical studie summarized in Tables 1 and 2. A convincing explanatio could not be proposed for the relation between early (mostl first trimester) maternal hypothyroxinemia and poor ne rodevelopmental outcome of the child. It was difficult t reconcile the very severe, and mostly irreversible, neurolo ical damage of cretins (with normal thyroid function whe iodine is supplied), with the successful prevention of seve brain damage by early postnatal treatment of congenit hypothyroidism (CH) babies, including athyrotics. The lac of protective effects of maternal T_3, compared with T_4, o

served in areas with severe ID, also posed many unanswered questions.

New findings, mostly obtained during the last 15 yr in experimental animals and in man, now clearly point to a role for the maternal transfer of thyroid hormone in brain development throughout fetal life and offer plausible explanations to the above questions. Despite these new findings and despite increasing acceptance of an important role for maternal T_4 in the prevention of severe brain damage in cases of CH, it is still stated that "Whether thyroid hormone is needed during the 1st trimester is less certain. If it is, it must be supplied by the mother, because none is secreted by the fetus until the middle trimester" (44). Because this point is essential for an understanding of the possible importance of first trimester FT_4 in fetal neurodevelopment, we will briefly review in Table 3 much of the information now available for experimental animals and for man.

Information obtained in experimental animals

Before onset of fetal thyroid function (FTF). Both T_4 and T_3 are available to early embryos, with very low concentrations being found when circulating concentrations in the mother are low. When this occurs, prenatal and postnatal developmental alterations can be shown. Nuclear receptors for T_3 (TRs) are also found in the early fetal brain, partially occupied by T_3, in rats, chicken, and sheep, with concentrations increasing during periods of very active cortical neurogenesis. Many cerebral genes sensitive to thyroid hormone deprivation have been identified, mostly in postnatal rats (45, 46), during a phase of brain development that corresponds to the second half of gestation and early postnatal period in man. The few studies reporting biological effects in the fetal rat brain at a phase of development corresponding to the first half of pregnancy in man have been restricted to a period coinciding or following onset of FTF at 17.5–18. days of gestation [E17.5-E18 (47–49)]. There is, however, increasing evidence that maternal thyroid hormone is already needed before onset of FTF; maternal hypothyroidism, as induced by treatment with goitrogens or thyroidectomy, interferes with the normal proliferation of some neurons usually completed by E12 (50). It also affects the migration of cells proliferating at E14-E15, normally reaching layer VI of the cortex by E16-E17 (51), and the cortical expression of several genes by E16 (52). Directly related to the possible role of maternal hypothyroxinemia without hypothyroidism is our very recent finding that an altered early migration of cortical cells can be observed in offspring of rats with severe ID (53). These dams have very low circulating T_4, but circulating T_3 is high enough to prevent "clinical" hypothyroidism.

After onset of FTF. The maternal to fetal transfer of thyroid hormone is not interrupted and continues to contribute to the thyroid hormone available to fetal tissues at term. Of special interest in the present context is the finding that a normal level of maternal T_4 is sufficient to protect a hypothyroid fetus preferentially from cerebral T_3 deficiency until birth. It is important to realize that maternal T_4 and T_3 are not equivalent with regard to this preferential protection of the hypothyroid fetal brain from T_3 deficiency. Without correction of the low maternal T_4, normal levels of T_3 in the maternal or fetal circulation have no protective effect because during fetal and postnatal development cerebral structures of the rat depend entirely on the local generation of T_3 from T_4 by type II 5′-iodothyronine deiodinase (D2), the activity of which is inversely related to the availability of T_4. Changes in the activity of 5-iodothyronine deiodinase (D3), which inactivates both T_3 and T_4, also play a role. During these periods

TABLE 3. Major findings from studies performed with experimental animals, and their possible relevance for man

	Experimental animals	Man
Before onset of FTF		
T_4 and T_3 present in embryonic and fetal fluids and tissues.	Rat (77–79), chicken (80), salmon (81), sheep (73)	Shown (82–84).
T_4 and T_3 are of maternal origin.	Rat (85), chicken (80), salmon (81)	Supported by correlation of T_4 in extra-embryonic cavity with maternal serum T_4 (83).
Nuclear receptors for T_3 are found, and partly occupied by T_3.	Rat (86–90), chicken (91, 92) and sheep (72)	Shown (93–95).
D2 and D3 are expressed in brain.	Rat (96), chicken (97)	Shown (98).
Adverse cerebral effects of low maternal T_4 early in pregnancy are being reported.	Rat (50–53), sheep (68). Reviews (85, 99, 100)	Supported by epidemiological and clinical studies (Table 1), and an in vitro study (101).
Between onset of FTF and birth		
Maternal transfer continues and contributes to fetal extrathyroidal thyroid hormone pools.	Rat (102–104)	Strongly suggested by earlier studies (42, 105–109). Shown by Vulsma *et al.* (110).
Brain T_3 is highly dependent on T_4 and the activities of D2 and D3, not on systemic T_3.	Rat (74–76, 96, 102, 103, 111–113)	Continuing role of T_4-regulated D2, and D3, in cerebral T_3 (114).
Normal maternal levels of T_4 protect the fetal brain from T_3 deficiency.	Rat (102, 103)	Supported by good results of early treatment with T_4 of newborns with CH, born from mothers with normal T_4.
Normal T_3 in hypothyroxinemic mother neither prevents cerebral T_3 deficiency, nor maintains T_3 homeostasis.	Rat (74–76, 102, 103, 113)	Supported by findings in ID cretins, whose mothers have low T_4, but normal circulating T_3 (Table 1).

of development, the contribution of systemic T_3 to the amount of T_3 in fetal cerebral structures is negligible. Fetal brain T_3 levels are also protected from excessive maternal circulating T_4, whereas cerebral T_3 homeostasis is not ensured when maternal circulating T_3 is excessive. Such results suggest that over-treatment of the mother with T_4 is potentially less damaging for the fetal rat brain than maternal hypothyroxinemia.

There is increasing evidence that the ontogenically programmed expression of D2 and D3, and the responses of these enzyme activities to thyroid hormone deficiency or excess, are the main mechanisms involved in the attainment of adequate concentrations of T_3 in different cerebral structures at different stages of development (54, 55), despite the fact that at each time point the circulating concentration of T_3 reaching all tissues is the same. This seems to be a general principle during development, even for other tissues and species (56–58). There is also an increasing consensus that an excess of thyroid hormones, especially T_3, may have adverse effects on the developing fetus and that throughout gestation the maternal-fetal unit has numerous mechanisms to avoid this. This would explain the high expression and activities of D3 in many structures of the maternal-fetal unit (58–62), especially the uterus and placenta (63). Sulfation of the iodothyronines, their deiodination, and further desulfation by sulfatases also seem to be playing important roles in tailoring the amounts of T_3 to changing temporal and spatial requirements during development (64, 65).

The abundant information obtained in pregnant sheep and newborn lambs has been reviewed by others (64, 66–69). Most of the available information has been obtained after midgestation, corresponding to late fetal and early neonatal brain development in man, and it supports the existence of numerous mechanisms that would regulate the amounts of circulating thyroid hormone in the fetus and newborn (69–71). In this species, placentation is epitheliochorial, quite different from that of man and of the rat. Despite this, limited transfer does exist in this species, as shown by the presence, before onset of FTF, of T_3 in the fetal brain, some of which is bound to the nuclear TR (72, 73). As in the rat, the hypothyroxinemia of iodine-deficient ewes before midgestation is accompanied by a reduced brain weight and changes in fetal brain morphology (68).

In summary, experimental findings, mostly obtained in the rat, provide an explanation for the lack of major irreversible brain damage at birth in the case of a human CH fetus from a normal mother. They also explain the early irreversible damage caused by ID, when both the mother and fetus are hypothyroxinemic throughout gestation (74–76), as well as the mechanisms involved in the preferential protective role, for the fetal brain, of T_4 over T_3.

Information obtained in man. Although man has an hemochorial placenta similar to that of the rat, transfer of thyroid hormones from mother to embryo and fetus may be quite different in both species. However, there are many findings that suggest that conclusions derived from experiments in the rat may be relevant to our understanding of early human brain development. These similarities are in Table 3.

Mechanisms preventing excessive amounts of thyroid hormones from reaching the fetal circulation are also operative in the human maternal-fetal unit. They involve both deiodinating enzymes, sulfotransferases, and sulfatases (64, 65,115–120.). Despite these mechanisms, maternal iodothyronines do reach the fetus. Thyroid hormones, specifically T_4, are already available to embryonic and fetal tissues before the onset of FTF (defined as the onset of secretion of the iodothyronines by the fetal thyroid). In man this occurs at midgestation (~18–22 weeks), coinciding with the development of the pituitary-portal vascular system. T_4 is found in first trimester coelomic fluid, which bathes the yolk sac, from the earliest date studied, namely at 6 weeks gestational age, in concentrations that correlate significantly with maternal circulating levels (83), whereas T_3 is barely detectable. Although coelomic fluid T_4 concentrations are low compared with those in adult blood, the FT_4 concentrations are comparable with those that are biologically effective in adults (84). T_3 has been quantified in purified extracts from human fetal brain as early as 9–10 weeks gestation (93, 94), and by midgestation the concentration of T_3 in the fetal brain reaches 34% of adult values and is, therefore, much higher than the level previously inferred from the very low circulating fetal T_3 [<10% of adult values (121)]. This cerebral T_3 is likely to have been generated locally from coelomic fluid T_4 of maternal origin. Brain D2 and D3 may already have important roles in the human fetal cortex before midgestation, with enzyme activities responding to maternal hypothyroxinemia (98).

Nuclear TRs are present in the brain of 10-week-old fetuses, increasing rapidly by 16 weeks, a period of very active cortical neurogenesis (93, 94). TR occupancy by T_3 was 25% throughout this period (94). As a result, the number of T_3-occupied TR units in the whole fetal brain increases about 500-fold between 10 and 18 weeks, a finding that confirms that maternal thyroid hormone does reach the human brain early in gestation. It has later been found that TRs are already expressed by 8 weeks of gestation, with ontogenic changes specific for brain regions and receptor isoforms (95).

As in the rat, maternal to fetal transfer of thyroid hormones continues until birth. Early evidence of this, following administration of radiolabeled or stable iodothyronines, was confirmed by Vulsma *et al.* (110). They showed that cord blood T_4 levels in newborns with a total organification defect were not negligible, with values that were 20–50% of those of normal newborns. This T_4 had to be of maternal origin because children with this congenital defect are unable to synthesize thyroid hormones. If data obtained in the rat can be extrapolated to man, this amount of T_4 in the fetal circulation ought to protect the brain of the CH fetus from T_3 deficiency until birth (103), although signs of thyroid hormone deficiency might be apparent in other tissues that are more dependent on systemic T_3 (*i.e.* delayed skeletal maturation, lung maturation, *etc.*).

Thus, all the conditions that in adults are known to result in biological effects of thyroid hormone are found in the human fetal brain, namely functioning D2, a maternal and/or fetal source of its substrate (T_4), and specific nuclear receptors partially occupied by the T_3 generated from T_4.

There is still very little information that might identify an early biological effect resulting directly from this T_3-TR interaction *in vivo*. A recent study performed *in vitro* with organ

cultures from 13- to 23-week human brains reports that the addition of T_3 stimulates cytoskeletal proteins, preferentially actin (101), but it remains to be shown that a deficiency of thyroid hormones *in vivo* would affect this process and do so during the first trimester. Until a cerebral end point of thyroid hormone action early in development is characterized, the long-lasting dispute concerning the mechanism(s) by which maternal hypothyroxinemia would negatively affect the fetal brain remains unresolved. Usually considered the most likely possibilities are: 1) poor placental function and maternal adaptation to pregnancy; 2) low levels of FT_4 available to the first trimester embryonic tissues; or 3) both. In our opinion, the evidence that is accumulating points to possibility 3, with a major role for 2. A major role for possibility 1 would not explain the marked neurodevelopmental damage of the neurological cretins whose mothers usually have normal circulating T_3 and are not clinically hypothyroid.

A unifying hypothesis for the findings summarized in Tables 1–3

Whichever mechanism(s) is involved, epidemiological and experimental studies strongly support that, inasmuch as it may affect the availability of T_4 (and consequently of T_3) to the developing brain, the main factor relating maternal thyroid function to poor neurodevelopmental outcome of the progeny is her hypothyroxinemia early in gestation, whether or not TSH is increased. Fine regulation of the amounts of T_3 ultimately generated from T_4 by different mechanisms would then tailor the availability of T_3 to temporal and spatial needs for thyroid hormone action in different brain structures, independently of circulating maternal or fetal T_3. These mechanisms, however, can only operate successfully when there is enough substrate, namely T_4. Persistence of maternal hypothyroxinemia later in pregnancy, when coupled to conditions that affect the capacity of the fetal thyroid to secrete sufficient T_4, and thus further decrease the availability of T_4 to the brain, would aggravate the neurodevelopmental damage. Figure 1 shows the proposed timing of insults to the developing brain in these conditions, as well as in CH and prematurity.

Severity and frequency of neurodevelopmental problems in the offspring of hypothyroxinemic, compared with hypothyroid, women. Table 4 attempts to quantify the magnitude of the cognitive

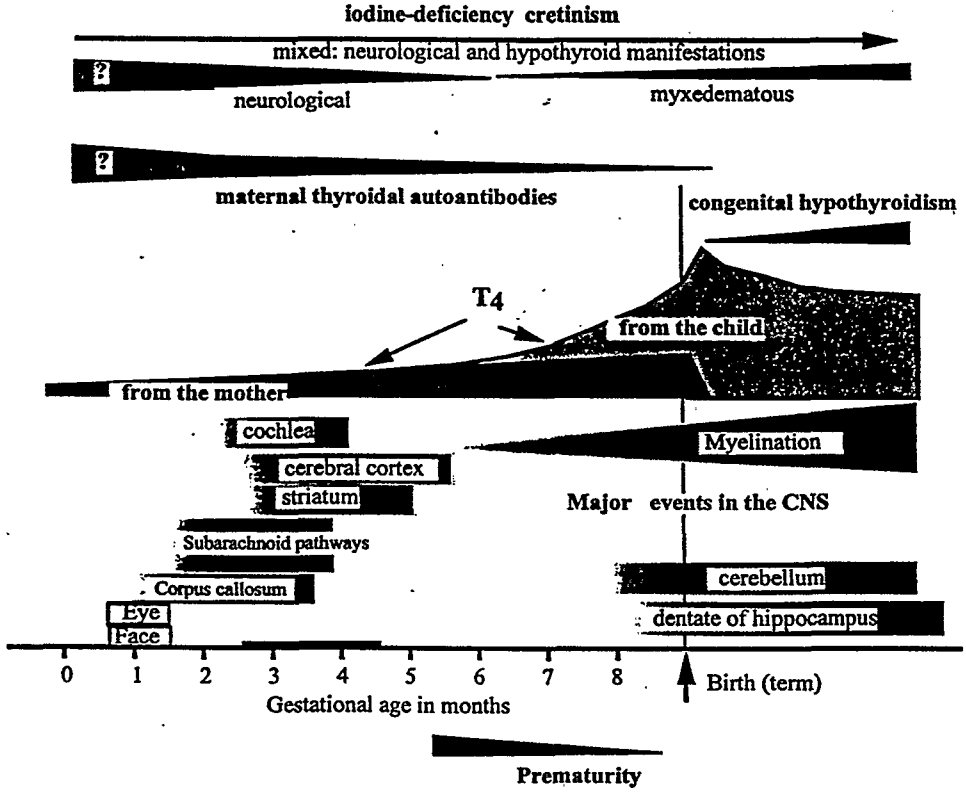

FIG. 1. Approximate timing of major insults to the brain resulting from hypothyroxinemia, superimposed on major neurodevelopmental events. Conditions resulting in early maternal hypothyroxinemia, combined to later impairment of the fetal thyroid, are the most damaging, with central nervous system (CNS) damage that is irreversible at birth. The most frequent cause is maternal ID and the presence of maternal AITDs. Unless ID is also present, the CNS damage in congenital hypothyroidism is preventable by early postnatal treatment because the normal maternal thyroxinemia has avoided damage to the brain until birth. If maternal hypothyroxinemia persists, normal maternal concentrations of T_3 do not protect the fetal brain because of its dependence on intracerebral regulation of local T_3 availability by deiodinating pathways using T_4 as a substrate. Interruption of the contribution of maternal T_4 in premature infants with an immature thyroid may also underlie their increased risk of neurodevelopmental problems, the more severe the earlier their birth. The *question mark* indicates that we do not know whether very early CNS development, corresponding to a period when the general morphogenesis of the pros encephalon (neurolation and segmentation) is being determined, is thyroid hormone sensitive or not.

TABLE 4. Comparison of data from different studies on neuropsychological development of the progeny born to women with thyroid abnormalities during pregnancy, such as hypothyroxinemia (whether or not ID is the cause), hypothyroidism, or positive antithyroid antibodies (anti-TPO)

Study (references) criteria for selection	I (122) I intake in area		II (20, 21) BEI			III (23) Anti-TPO		IV (3) 1st trimester FT4		V (1) 2nd trimester TSH		
Group	C No ID	A ID	C Normal	A Low[a]	B Low, treated	C Neg. (−)	A Pos. (+)	C >10th%	A ≤10th%	C <98th%	A ≥98th%	B ≥98th% treated
$\bar{x} \pm$ SD	100 ± 15	86.5 ± 15	96.6 ± 15	91.9	105.0	104.3 ± 13.3	93.8 ± 15.4	98.6 ± 14.7	88.3 ± 15.3	107 ± 12	100	111
$\bar{x}_A - \bar{x}_C$		−13.5		−4.7			−10.5		−10.3		−7.0	
$\bar{x}_A - \bar{x}_B$					−13.1							−11.0
% with IQ ≤85[b]	15.9	46.0	16	33	0	15.9	31.6	18	50	5	19	0
% with IQ ≤70	2.3	13.7				2.3	8.3	1.0	5.0			
OR for IQ ≤85		4.5		2.6			4.8		4.6		4.5	
95% C.I.		3.7–5.6		1.3–5.1			3.7–6.3		2.4–8.7		1.6–12.5	

BEI, Butanol extractable iodine, equivalent to the I present in serum as T_4; OR, odds ratio; CI, confidence intervals of the OR.

[a] Low BEI values were below the range for euthyroid pregnant women at a comparable stage of pregnancy.

[b] Includes all children with IQ ≤85, without subtracting those with IQ ≤70.

limitation of the children born from mothers with inadequate T_4, FT_4, TSH, or anti-TBO antibody titers during pregnancy, as assessed from data provided by the authors of the different studies, or from our calculations, using statistics reported in the studies or provided by personal communication (Dr. V. Pop). We have "normalized" the IQ scores given in different studies to those of the test norm, taken as 100 ± 15, to calculate the frequency of children with IQ scores less than or equal to 85 (mean-1 SD; feeble-minded or mentally defectives) or less than or equal to 70 (mean-2 SD; mentally retarded). Most studies provide information regarding the frequency of neurodevelopmental scores that are less than or equal to 85, but only a few indicate separately the frequency of those less than or equal to 70. The metanalysis of results from studies in iodine-deficient areas do not include cretins, but only the apparently "normal" population. All of the studies have applied corrections for likely confounding factors.

The largest effects, as assessed from the loss of IQ points in children from the untreated selected pregnant women (*vs.* their controls) and from the corresponding odds ratios, are associated with the use of ID (Study I), low first trimester FT_4 (Study IV), and positivity of anti-TPO antibodies during pregnancy (Study III) as criteria for selection of the women. Although data from the study by Haddow *et al.* (1), using second trimester elevated TSH values for the selection, do not at first seem to be far behind, results summarized in Table 5 show an important difference with respect to Studies I-IV, namely, the 5- to 7-fold smaller number of children at risk who are, thus, identified. This is related to the lower frequency with which an increased second trimester TSH is found in pregnant women, compared with the frequency with which women are selected using the other criteria: ID, low maternal T_4 or FT_4, and/or autoimmune thyroid disorders. Table 5 also highlights another important issue; although the mean decreases in IQ points referred in the different studies are less severe than previously reported for inadequately treated CH babies (30), the number of potentially affected children might be 150–200 times greater.

Therefore, we do not fully agree with the proposal that screening on the basis of an elevated TSH (1, 44) would be the most adequate procedure to identify pregnant women at risk of bearing children with neurodevelopmental problems related to an inadequate maternal thyroid hormone status. Even the determination of TSH during the first trimester might not be adequate, because the maternal thyroid is then affected by the TSH-like activity of the high levels of hCG and first trimester TSH responses may be blunted (125). Moreover, some pregnant women with increased TSH might have normal FT_4 levels, and their inclusion in the study group may affect the differences found between the neurodevelopmental outcome of the children from this group and that of the control children. The same might occur if the control group includes women with normal TSH, but who might have a low first trimester FT_4 (126). High maternal anti-TPO antibodies, also related to poorer neuropsychological development of the child, are not necessarily accompanied by elevated maternal circulating TSH (23). The findings briefly summarized above from premature hypothyroxinemic babies also indicate that they would not be detected using a neonatal increase in circulating TSH as selection criterion.

TABLE 5. Comparison of the estimated frequencies of newborns with CH with those of children with impaired psychomotor development, born to women with alterations of thyroid hormone status during pregnancy, detected using different criteria for selection. For these calculations, we have used data reported in different studies (references in *parentheses*) and data shown in Table 4

Study	CH	I	II	III	IV	V
Criteria for selection	TSH of newborn high, and/or T_4 low	Severe ID area	Low BEI	Anti-TPO + during pregnancy	1st trimester FT_4 ≤10th percentile	2nd trimester TSH >98th percentile
% of pregnant women selected (not treated)		All?	9.4% (17)	8% (21)	10% (22)	2.5% (1, 126)
% of newborns at risk	0.025–0.030%	46%	1.3–3.1%	2.5%	5%	0.47%
Frequency of progeny with IQ ≤85[a]	1:3000–1:4000	1:2	1:32–1:76	1:39	1:30	1:150
Frequency of progeny with IQ ≤70		1:7		1:150	1:250	

[a] Includes all children with IQ ≤85, without subtracting those with IQ ≤70.

Thus, we conclude that present information permits an answer regarding points 1 and 2 of the aim of the present comments, and we, therefore, suggest that the very pertinent question asked by Utiger (44) regarding the frequency of hypothyroidism in pregnant women ought to be modified and referred to the frequency of first trimester maternal hypothyroxinemia.

An even more important reason for our present comments is that the major cause of maternal hypothyroxinemia worldwide is ID, as clearly stressed by Utiger (44) in his recent editorial accompanying the paper by Haddow *et al.* (1). Contrary to the usual findings in patients with primary hypothyroidism, low circulating T_4 levels are not necessarily accompanied by elevated TSH in situations of ID, especially if it is mild or moderate. The thyroid gland is able to maintain euthyroidism by responding to ID through intrathyroidal autoregulatory mechanisms that do not require an increased circulating TSH, such as an increased thyroidal blood-flow and thyroid volume, increased thyroidal iodine clearance, and preferential thyroidal synthesis and secretion of T_3 over T_4, and increased intrathyroidal half-life of iodine-containing compounds. Circulating T_4 decreases and serum thyroglobulin (Tg) increases, but TSH is usually normal both in goitrous and nongoitrous subjects (127), very probably because circulating T_3 is normal or elevated. Enlargement of the thyroid and increased circulating Tg are more reliable parameters of ID than increased TSH (128). Even in areas of very severe ID, where neurological cretins were born, TSH levels (if increased), were not as high as in clinically hypothyroid patients from iodine-sufficient areas (129, 130) and were not related to the developmental outcome of the child (15).

The frequency of maternal hypothyroxinemia is likely to be much higher in areas of ID. In areas of grade III (severe) ID, 43% of the pregnant women had a low PBI (<6 μg/dL), with the protein-bound iodine values being positively correlated with neurodevelopmental outcome. Even in more developed countries, the frequency of maternal first trimester hypothyroxinemia may be higher than in Holland where Pop *et al.* (3) carried out their study, because of lower iodine intakes. Thus, in the very thorough studies performed by Glinoer at al (125) in Brussels, where ID is moderate (grade II; median urinary I in pregnant women being 56 μg/L), up to 30% of the women had low first trimester FT_4 concentrations, which is almost 10 times the frequency of elevated TSH (2.3%) and 6 times the frequency of high titers of thyroid autoantibodies (5.2%). In Madrid (131), where ID is milder than in Brussels (the median urinary I being 90 μg/L throughout pregnancy), the number of women with first trimester FT_4 levels that are less than the 10th percentile values for women receiving an adequate iodine supplement was increased 2-fold, again mostly without an increase in circulating TSH more than or equal to the 98th percentile, or an increase of women with positive thyroid autoantibodies. The median urinary I of these supplemented women was 190 μg/L, which would correspond to a daily 24-h excretion of 270 μg I, provided we assume a mean diuresis of 1.4 l. Although their FT_4 decreased during pregnancy, as repeatedly reported by others (125), it was significantly higher, throughout gestation, than that of the women who did not receive the I supplement. Indeed, in each trimester FT_4 was significantly correlated with the urinary I, independently of gestational week or T_4-binding globulin concentrations. None of the women on I supplements had goiter at delivery, in contrast to 24% of those not receiving them. This information would suggest that the iodine requirements of the pregnant woman are 200–300 μg per day, at least in areas where the previous borderline ID has not permitted the accumulation of iodine stores sufficient to face her increased needs and those of the fetus. These amounts are almost double those recommended for children and for nonpregnant or nonlactating adults.

The studies from Brussels and Madrid suggest that these women are likely to be hypothyroxinemic during pregnancy, unless given iodine supplements from the onset or before (44, 132, 133). As pointed out by Utiger (44), the United States might also be facing more problems related to ID than previously realized. His comment is based on the recent study regarding iodine nutrition in the United States (134), which has decreased markedly during the last 20 yr: the median urinary I has decreased from 320 μg/L to 145 μg/L. As many as 15% of women of childbearing age had concentrations below 50 μg/L. North Americans are, therefore, also included in the recommendation that iodine supplements be taken during pregnancy, from the very beginning, or even better, before its onset (44).

Moreover, as already discussed, ID does not necessarily cause hypothyroidism with increased TSH and may not be detected using an elevated TSH as criterion for selection of pregnant women with increased risk of progeny with neurodevelopmental deficits. Nonetheless, it may result in de-

creased maternal FT_4 in a relatively large number of women and to the ensuing increased risk of psychomotor defects (3). That this relative ID is so easily preventable, and at such a small cost, makes it all the more frustrating that the general public and the medical community are not fully aware of the problems that ID may continue to pose for future generations.

Although our present comments have been focused mainly on the relationship between inadequate maternal thyroid function, especially hypothyroxinemia, and neurodevelopmental problems of her child, other negative effects cannot be overlooked, such as an increased rate of spontaneous abortions, placental disruptions, fetal distress, malformations, prematurity, decreased birth weight, poorer perinatal outcome, and pregnancy-induced hypertension (20, 22, 26, 27, 135–138). Those caused by autoimmune thyroid disorders (AITDs) have been extensively studied and reviewed by Glinoer (4, 125, 139), both with respect to subclinical and overt hypothyroidism and to subclinical and overt hyperthyroidism and transient gestational hyperthyroidism. His conclusion is that systematic screening for autoimmune disorders and for TSH more than 4 or less than 0.1 mU/mL early in pregnancy is justified by present evidence, considering both their frequency and the increased risk of adverse pregnancy outcome and perinatal morbidity, and the benefits for the child and for the future health of the mother of adequate treatment. We should again like to remark that this conclusion was already reached by Glinoer (4, 125, 139) without taking into account that high titers of maternal anti-TPO antibodies during pregnancy are also a marker of impaired neuropsychological development of the child (23), or that the latter outcome is very poor in the progeny of untreated mothers with high titers of TSH receptor blocking antibodies (35, 140, 141).

To screen or not to screen, that is the question. Presently available epidemiological and experimental evidence strongly supports the need for an increasing widespread attention to maternal thyroid status during pregnancy. Glinoer (125, 139) has already proposed systematic screening algorithms (4) for AITDs and subclinical and overt hypo- and hyperthyroidism early in pregnancy, as well as the ensuing treatment protocols. The proposed screening program is based on the determination of positive anti-TPO antibodies (also positive anti-Tg antibodies if economically feasible) and TSH more than 4 or less than 0.1 mU/mL, preferably at 12 weeks of gestation. These algorithms do not include tests for TSH receptor blocking antibodies, despite the high risk of the very severe neurodevelopmental damage to the offspring, possibly because of their low incidence [1:180 000 pregnancies (142)] and because the bioassays developed so far are not easily performed. In view of the evidence we have reviewed here, however, which shows a relationship between early maternal hypothyroxinemia and poor neurodevelopmental outcome, we believe that inclusion of screening for low FT_4 as well would considerably increase the benefits of the program proposed by Glinoer (4).

The cut-off points of the FT_4 values needed to establish the degree of hypothyroxinemia at different gestational ages (and using different commercially available kits) remains to be defined, ensuring it is done in pregnant women with a confirmed iodine intake of 200–300 μg/day (145–220 μg I/L urine) or more. Inclusion in the reference group of women on an insufficient iodine intake would underestimate the lowest 10th percentile.

How to correct the hypothyroxinemia in time to avoid neurodevelopmental problems might also require further controlled studies or screening trials, as stressed in a recent editorial by Pop *et al.* (123). However, despite the different methodologies and study designs used in the studies performed by Man and Serunian (20, 21) and by Pop *et al.* (3) in women who were reportedly iodine sufficient (from Rhode Island and The Netherlands), there are some striking similarities in the IQ scores of their children, and the frequency of values less than or equal to 85. But, only the studies from Man and Serunian (20, 21) included a group of women whose low BEI was promptly corrected by treatment with thyroid extracts. It is interesting that none of the children born from these mothers had IQ scores less than or equal to 85, and the mean IQ was actually higher than that of the progeny of women without hypothyroxinemia, strongly suggesting that treatment would be effective.

A clear definition of the cut-off values of the proposed screening tests and the most appropriate treatment of positive cases were also lacking when neonatal thyroid screening programs were started: despite that they have become a clear example of success in the prevention of mental retardation. The proposed biochemical markers are all presently available as blood spot tests (143). Thus, linking thyroid screening of pregnant women to the logistic facilities developed for local neonatal thyroid screening programs might considerably improve the cost to benefit ratio, because the biochemical tests *per se* do not constitute the major expense of such programs.

Glinoer's proposal (4) for screening at 12 weeks of gestation seems reasonable for hypothyroxinemia as well, because an earlier first prenatal visit is highly unlikely. Blood samples would then be taken for the determination of FT_4, anti-TPO (and possibly anti-Tg) antibodies, and for TSH. Women who were not screened during this period should still be tested later in gestation because potential benefits might still be obtained, especially if the condition is caused by an autoimmune disorder that may also affect the fetal thyroid. Screening before pregnancy would probably benefit those women presenting with high antibody titers, abnormal values of TSH, or hypothyroxinemia, but may well be insufficient: pregnancy itself may be the factor that contributes to an inadequate availability of T_4 for the fetus, unmasking an underlying thyroid failure, or an iodine intake insufficient to meet the increased maternal and fetal needs.

For the future assessment of the results of the inclusion of FT_4 in the screening program, it would be important to evaluate the iodine intake of the pregnant woman by determining iodine and creatinine in casual urine samples taken on the same day as the blood samples. An inexpensive method for the determination of urinary iodine, easy to perform and not requiring costly hardware, is presently available, making these determinations easy to incorporate into any biochemical clinical laboratory or neonatal thyroid screening program (144). We are currently attempting to develop a method

for the determination of iodine in urine spots on filter paper. These data would later disclose the proportion of women from different regions in whom hypothyroxinemia is related to ID and, therefore, easily prevented or corrected without further treatments.

At this first prenatal visit, all pregnant women would immediately start supplementing their usual diet, throughout pregnancy and lactation, with 200–300 μg I/day, either in the form of KI or KIO3 tablets or vitamin-mineral mixtures (44, 145). Even if the urinary iodine excretion value later indicates that the iodine intake was already adequate for pregnancy, the supplementation would not harm. It has, indeed, been shown that the administration of much larger amounts of iodine during any stage of pregnancy, such as those delivered by ingestion or injection of iodized oils, does not harm fetal neurodevelopment (146, 147). If the TSH data at screening suggest thyroid hyper function, supplementation could be stopped. Inclusion of iodine supplementation into the program is likely to be much more effective in ensuring permanent correction of maternal iodine deficiency than mere information programs to the general public and the medical profession.

If the results of the screening tests indicate abnormal values of either thyroid autoantibodies, TSH, or both, the algorithms outlined by Glinoer (4) could be implemented. If the only abnormal value is a FT_4 that is low for gestational week, a new blood sample would be withdrawn within 2 weeks for the determination of serum FT_4. Correction, or amelioration, of the FT_4 levels would suggest that supplementation of the diet with iodine is sufficient. If, despite iodine supplementation, FT_4 remains persistently lower than the 10th percentile value for normal pregnant women with a confirmed adequate iodine intake at comparable weeks of gestation, additional treatment with T_4 might be considered pertinent to ensure the FT_4 levels that have been found to be normal in iodine-sufficient women at the same stage of pregnancy.

Summary. Screening programs for the identification of pregnant women with hypothyroxinemia, hypothyroidism, AITDs, or hyperthyroidism are likely to pose more organizational problems than the screening of neonates for CH. However, the much greater frequency with which alterations of maternal thyroid function are detected, which potentially jeopardize the outcome of pregnancy and increase the risk of neurodevelopmental impairment of the offspring, ought to encourage their implementation. Fukushi *et al.* (143) have recently reported that a screening program of the thyroid function of pregnant women from the Sapporo region in Japan was initiated in 1991, and data are available for 70,632 women. The authors conclude it is a useful program, despite the fact that thyroid disease among pregnant women is likely to be lower in Japan than in other countries (hypothyroxinemia due to ID is highly unlikely). These programs are likely to greatly increase the awareness of the general medical profession of the importance of the prevention of ID during pregnancy and also lead to a much needed closer collaboration between gynecologists and endocrinologists for adequate treatments following well-defined protocols (2, 4).

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Call for Papers for the Special June 2001 Issue

At the request of Endocrine Society president Dr. Benita Katzenellenbogen, *The Journal of Clinical Endocrinology & Metabolism* and the other Endocrine Society journals will devote their June 2001 issues to topics in Reproductive Hormones and Human Health. This theme will also be emphasized at the 83rd Annual Meeting of The Endocrine Society in Denver, Colorado, June 20–23.

The editors of *The Journal of Clinical Endocrinology & Metabolism* are seeking submissions for this special issue. Manuscripts reporting investigations of male or female reproduction in a variety of organ systems, including the skeleton, gastrointestinal tract, cardiovascular, mammary, immune and neuroendocrine systems, as well as the gonads and reproductive tracts, are welcome.

The deadline for submissions is DECEMBER 15, 2000. Please indicate explicitly in your cover letter that you wish to have the manuscript considered for the June 2001 issue.